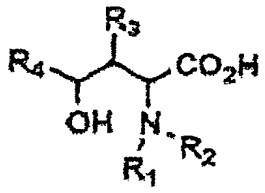
CLAIMS

1. A method of preparing diastereoisomers and enantiomers of 4-hydroxyisoleucine and derivatives thereof of general formula I



I

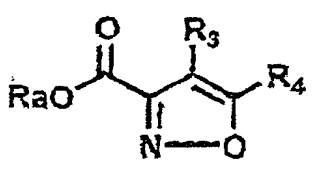
in which R_1 and R_2 represent

· a hydrogen atom or

· one of R_1 or R_2 represents a hydrogen atom and the other substituent is a radical R_a, an acyl group $-COR_a$, in particular acetyl, or else a functional group $-COOR_a$, $-SO_2R_a$ or $-N(R_a,R_b)$, R_a and R_b, which are identical or different, being an optionally substituted linear or branched C1-C12 alkyl radical, an optionally substituted aryl group containing one or more aromatic rings, comprising 5 to 8 C, or aralkyl, the alkyl substituent and the aryl group being as defined above, or

· R_1 and R_2 both represent a substituent as defined above,

characterized in that it comprises reducing an isoxazole derivative of formula II



II

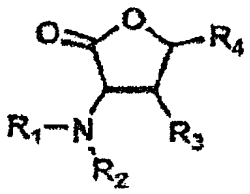
in which

· R_a is as defined above, and

· R_3 represents a hydrogen atom or R_a, and

· R_4 exhibits the significations of R_a, with the exception of a hydrogen atom,

under conditions leading directly to derivatives of formula I or to at least one lactone of structure III

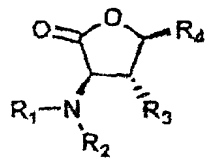


III

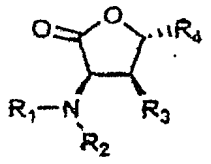
in racemic form(s), or an enantiomerically enriched mixture, followed by the opening, under basic conditions, in a protic or aprotic solvent, of the required lactone or lactones and, if necessary, the separation of the required form.

2. The method of claim 1, characterized in that the lactone ring is opened by means of LiOH in THF.

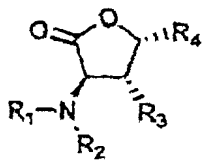
3. The method of claim 1 or 2, characterized in that the lactone of structure III is obtained by reducing said isoxazole derivative of formula II, leading to a mixture containing 4 lactones L-1, L-2, L-3 and L-4:



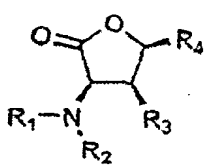
L-1



L-2



L-3



L-4

4. The method of claim 3, characterized in that, where R_3 represents a hydrogen atom in the isoxazole of formula II, a group R_a is introduced subsequently into the intermediates obtained.

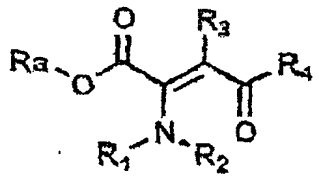
5. The method of claim 1 or 2, characterized in that the desired lactone or lactones is or are separated in racemic or in enantiomerically pure form, the preparation of one of the lactones and/or one of the enantiomers being promoted by the catalyst and the conditions that are used.

6. The method of any one of the preceding claims, characterized in that the lactones in which R_1 and/or R_2 represent a hydrogen atom are substituted, in particular alkylated, carbamylated, sulfonylated or acylated, especially acetylated.

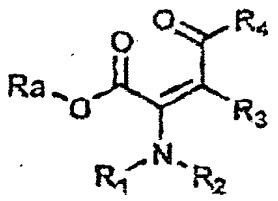
7. The method of claim 1, characterized in that it comprises reducing an isoxazole of formula II in which OR_a represents a group amenable to hydrogenolysis, such as the benzyl group, this reduction step being carried out in a basic medium when R_a is other than a benzyl group.

8. The method of any one of the preceding claims, characterized in that the intermediates formed during the step of reducing the isoxazole derivative of formula II are isolated.

9. The method of claim 3, characterized in that operation takes place in an ethanol/water medium, to which a solution of Raney nickel in ethanol and the isoxazole derivative of formula II are added, and the mixture is purged with hydrogen, the reaction medium being subsequently stirred under a hydrogen pressure of the order of 1 atmosphere at ambient temperature, giving the derivatives IV and V:

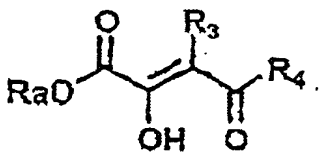


IV



V

it being possible for the compounds IV and V to be obtained, alternatively, directly from the compound of formula VI.

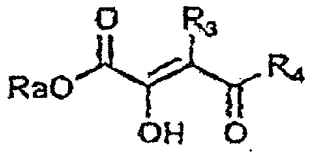


VI

10. The method of claim 9, characterized in that the compound V is subjected to the action of a reduction catalyst in a solvent in the presence of a hydrogen source.

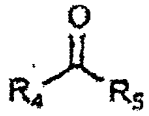
11. The method of claim 9, characterized in that the compound IV or V is subjected to the action of a homogeneous reduction catalyst, of a chiral or achiral ligand, in the presence of an organic solvent, of triethylamine and a hydrogen source, or, alternatively, the compounds IV or V are subjected to reduction in an ethanol/water mixture in the presence of $NaBH_4$ and $CeCl_3 \cdot 7H_2O$.

12. The method of any one of the preceding claims, characterized in that the isoxazole derivative of formula II is obtained by reacting a hydroxylamine with a 4-keto-2-hydroxy-2-butenoic acid derivative of formula VI:

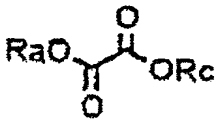


VI

13. The method of claim 12, characterized in that the 4-keto-2-hydroxy-2-butenoic acid derivative is obtained by condensing a ketone VII and an oxalate derivative VIII:



VII



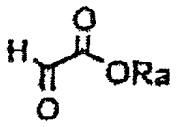
VIII

in these formulae, R_5 represents an alkyl, such as ethyl or methyl, alkylaryl, vinyl or substituted vinyl radical, R_4 and R_a are as defined above. R_c exhibits the significations given by R_a and may be is identical to or different from R_a.

14. The method of claim 13, characterized in that the ketone used is butanone.

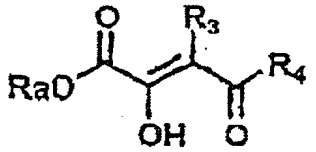
15. The method of claim 13, characterized in that the ketone used is acetone, leading to the 4-keto-2-hydroxy-2-butenoic acid derivative of formula VI in which R_3 is a hydrogen atom and R_4 represents CH_3.

16. The method of claim 13, characterized in that the 4-keto-2-hydroxy-2-butenoic acid of formula VI is obtained by operating in accordance with the Baylis-Hillmann reaction, by reacting methyl vinyl ketone with a glyoxalate of formula IX,



IX

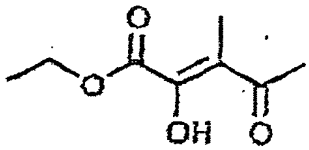
followed either by a step of isomerization to compound VI, in the presence of transition metal catalyst, or by reduction of the double bond and then oxidation of the OH function.



VI

17. A method of preparing (2S, 3R, 4S)-4-hydroxyisoleucine, characterized in that it comprises the steps of

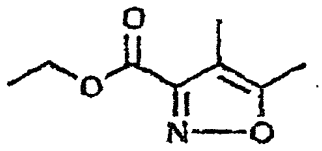
a) synthesis of an ester of pent-2-enoic acid of formula X



X

either by reacting butanone with ethyl oxalate or by condensing methyl vinyl ketone with ethyl glyoxalate, followed, without purification, by an isomerization reaction or by a reduction/oxidation sequence;

b) the ester of pent-2-enoic acid obtained reacts with hydroxylamine to form the isoxazole derivative of formula XI,



XI

c) the reduction of the isoxazole derivative obtained to give the lactones I-1 to I-4,

I-1 I-2 I-3 I-4

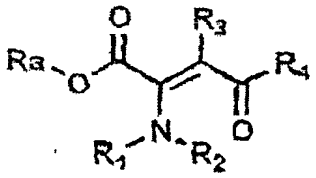
d) the separation of lactone I-1 to I-4 in racemic form, followed by

e) the separation of the enantiomer, leading to the compound A by opening of the lactone, and by

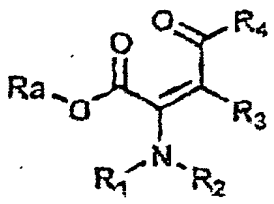
f) the opening of the lactone ring.

18. As new products,

the intermediate compounds of formulae IV and V,



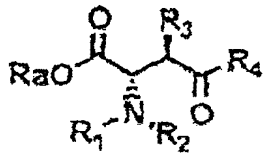
IV



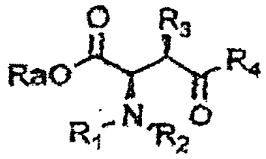
V

in which one of R_1 and R_2 represents H, the other being other than H,

the compounds corresponding to C-1 and C-2, of formulae



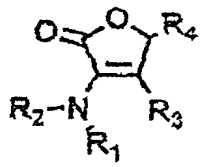
C-1



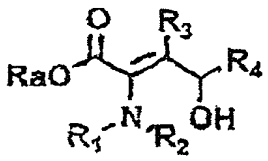
C-2

the substituents being as defined above irrespective of R_1 and R_2,

· the compounds E-1 and E-2, corresponding to the formulae



E-1



E-2

in which the substituents are as defined above in relation to the formulae IV and V.